PATENT COOPERATION T. ATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 26 May 2000 (26.05.00)	
International application No. PCT/EP98/06298	**Applicant's or agent's file reference** C 2086 PCT
International filing date (day/month/year) 02 October 1998 (02.10.98)	**Priority date** (day/month/year)
Applicant REIMANN, Hansjörg et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

06 April 2000 (06.04.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer C. Villet
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Claims

1. A polynucleotide encoding a fusion protein which is stable in a cell, said fusion protein comprising:
   (a) a first (poly)peptide; and
   (b) a second (poly)peptide which co-precipitates a chaperone.

2. The polynucleotide of claim 1, wherein said first (poly)peptide is unstable in a cell.

3. The polynucleotide of claim 1 or 2, wherein said first (poly)peptide is or comprises an epitope and/or a functional and/or structural domain of a protein, and/or a mutated or truncated variant of a protein.

4. The polynucleotide of any one of claims 1 to 3, wherein said chaperone belongs to the family of heat shock protein (hsp)70 chaperones.

5. The polynucleotide of claim 4, wherein said chaperone is hsp73.

6. The polynucleotide in particular of any one of claims 1 to 5, wherein said second (poly)peptide is a viral T antigen carrying an internal and/or C-terminal deletion.

7. The polynucleotide of claim 6, wherein the function and/or structure of the N-terminal J domain of said viral T antigen is maintained.

8. The polynucleotide of claim 6 or 7, wherein said viral T antigen is a viral large T antigen.

9. The polynucleotide of claim 6 or 7, wherein said viral T antigen is SV40 T antigen.

10. The polynucleotide of claim 8, wherein said viral large T antigen is SV40 large T antigen.

11. The polynucleotide of claim 10, wherein the about 300 C-terminal amino acids of said SV40 large T antigen are deleted.

12. The polynucleotide of claim 10 or 11, wherein said SV40 large T antigen contains amino acids 1 to 272.

13. The polynucleotide of any one of claims 10 to 12, wherein the internal deletion comprises at least part of the nuclear localisation signal.

14. The polynucleotide of claim 13, wherein amino acids 110 to 152 are deleted.

15. The polynucleotide of any one of claims 1 to 14 further encoding a tag.

16. The polynucleotide of any one of claims 1 to 15, wherein said first and second (poly)peptide are linked via a protease cleavage site.

17. A vector comprising the polynucleotide of any one of claims 1 to 16.

18. The vector of claim 17, wherein said polynucleotide is operatively linked to an expression control sequence.

19. A host cell comprising the polynucleotide of any one of claims 1 to 16, or the vector of claim 17 or 18.

20. The host cell of claim 19 which is a eukaryotic or prokaryotic cell.

21. A method for the production of the fusion protein as defined in any one of claims 1 to 16, said method comprising:

(a) culturing the host cell of claim 19 or 20 under conditions that allow the

synthesis of said fusion protein; and

(b) recovering said fusion protein from the culture.

22. The method of claim 21 further comprising the step of separating said fusion protein from complexed chaperones.

23. A fusion protein encoded by the polynucleotide of any one of claims 1 to 16, or the vector of claim 17 or 18, or obtainable or obtained by the method of claim 21 or 22.

24. A method for the production of a first (poly)peptide as defined in claim 2 or 3, said method comprising:

(a) culturing the host cell of claim 19 or 20 under conditions that allow the synthesis of a fusion protein as defined in claim 16;

(b) recovering said fusion protein from the culture; and

(c) separating said second (poly)peptide from said fusion protein by proteolytic cleavage.

25. A method for the production of a complex comprising the fusion protein of claim 23 and a chaperone as defined in claim 4 or 5, said method comprising:

(a) culturing the host cell of claim 19 or 20 under conditions that allow complex formation of said fusion protein with said chaperone; and

(b) recovering said complex from the culture.

26. A method for the production of an antibody directed against a first (poly)peptide as defined in claim 2 or 3, said method comprising administering in an amount sufficient to induce a humoral immune response the polynucleotide of any one of claims 1 to 16, the vector of claim 17 or 18, the fusion protein of claim 23, the first (poly)peptide obtainable or obtained by the method of claim 24, and/or the complex obtainable or obtained by the method of claim 25 to a subject.

27. A method of immunizing a subject, said method comprising administering in an

amount sufficient to induce a humoral and/or cellular immune response the polynucleotide of any one of claims 1 to 16, the vector of claim 17 or 18, the fusion protein of claim 23, the first (poly)peptide obtainable or obtained by the method of claim 24, and/or the complex obtainable or obtained by the method of claim 25 to said subject.

28. A kit comprising:
    (a) the polynucleotide of any one of claims 1 to 16;
    (b) the vector of claim 17 or 18;
    (c) the host cell of claim 19 or 20;
    (d) the fusion protein of claim 23;
    (e) the first (poly)peptide obtainable or obtained by the method of claim 24;
    (f) the complex obtainable or obtained by the method of claim 25; and/or
    (g) the antibody obtainable or obtained by the method of claim 26.

29. A diagnostic composition comprising the polynucleotide of any one of claims 1 to 16, the vector of claim 17 or 18, the fusion protein of claim 23, the first (poly)peptide obtainable or obtained by the method of claim 24, the complex obtainable or obtained by the method of claim 25, and/or the antibody obtainable or obtained by the method of claim 26.

30. A method for the detection of the presence of an epitope comprised in a (poly)peptide as defined in claim 2 or 3, said method comprising:
    (a) contacting the fusion protein of claim 23 or the first (poly)peptide obtainable or obtained by the method of claim 24 with an antibody or a cytotoxic T-lymphocyte (CTL) under conditions that allow binding of said antibody or CTL to said epitope; and
    (b) detecting whether the antibody or CTL has bound to said epitope.

31. The method of claim 30, wherein said antibody or CTL is derived from an individual infected with a pathogen.

32. The method of claim 30 or 31, wherein the first (poly)peptide of said fusion protein or said first (poly)peptide obtainable or obtained by the method of claim 24 is derived from a pathogen.

33. A pharmaceutical composition comprising the polynucleotide of any one of claims 1 to 16, the vector of claim 17 or 18, the fusion protein of claim 23, the first (poly)peptide obtainable or obtained by the method of claim 24, the complex obtainable or obtained by the method of claim 25, and/or the antibody obtainable or obtained by the method of claim 26, and, optionally, a pharmaceutically acceptable carrier and/or diluent.

34. The pharmaceutical composition of claim 33 which is a vaccine.

35. The pharmaceutical composition of claim 34, wherein said vaccine induces a humoral and/or cellular immune response.

36. Use of the polynucleotide of any one of claims 1 to 16 or the vector of claim 17 or 18 for the production of an antibody directed against a first (poly)peptide as defined in claim 2 or 3.

37. Use of a (poly)peptide comprising an epitope detected by the method of any one of claims 30 to 32 or a complex produced by the method of claim 25 for the production of an antibody.

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12N 15/62, C07K 14/025, 16/08, 16/18, G01N 33/50, C12Q 1/68, A61K 39/295

A1

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DE (Utility model), DK, EE, ES (Utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: METHOD FOR THE PRODUCTION OF (POLY)PEPTIDES BY USING TRUNCATED VARIANTS OF THE SV40 LARGE T ANTIGEN WITH AN INTACT N TERMINUS

(57) Abstract

The present invention relates to a polynucleotide encoding a fusion protein which is stable in a cell, said fusion protein comprising a first (poly)peptide and a second (poly)peptide which co–precipitates a chaperone. The present invention also relates to a vector comprising the polynucleotide of the invention, a host cell comprising the polynucleotide or the vector of the invention, and a method for the production of the fusion protein of the invention. Also described are methods for the production of said first (poly)peptide, of a fusion protein/chaperone complex, and of an antibody directed against said first (poly)peptide, as well as a method of immunizing a subject with the polynucleotide, the vector, the fusion protein, said first (poly)peptide and/or said fusion protein/chaperone complex of the invention. In addition, the present invention relates to a kit and a diagnostic composition comprising the polynucleotide, the vector, the host cell, the fusion protein, the first (poly)peptide, the fusion protein/chaperone complex and/or the antibody of the invention. The present invention, furthermore, relates to a method for the detection of the presence of an epitope comprised in a (poly)peptide. Additionally described is a pharmaceutical composition comprising the polynucleotide, the vector, the fusion protein, the first (poly)peptide, the antibody, and/or the complex of the present invention and, optionally, a pharmaceutically acceptable carrier and/or diluent, said pharmaceutical composition being preferably a vaccine. Finally, the present invention relates to the use of the polynucleotide or the vector of the invention for the production of an antibody directed against said first (poly)peptide, and the use of a (poly)peptide comprising an epitope detected by the method of the present invention or a complex produced by the method of the invention for the production of an antibody.

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INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/EP 98/06298

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/62 C07K14/025 C07K16/08 C07K16/18 G01N33/50
C12Q1/68 A61K39/295

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K G01N C12Q A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	SCHIRMBECK R. ET AL: "Truncated or chimeric endogenous protein antigens gain immunogenicity for B cells by stress protein-facilitated expression." EUROPEAN JOURNAL OF IMMUNOLOGY, (MAY 1999) 29/5 (1740-1749)., XP002107329 see the whole document	1-25,27, 30
X	WO 93 19091 A (AMRAD CORP LTD) 30 September 1993 see page 4, last paragraph - page 5, paragraph 1 see page 11 see page 14-17	1-12, 15-25,30
Y	see page 19; claims 8-10	13,14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 June 1999	12/07/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Espen, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	COULOMBE, JOSEE ET AL: "Activation of simian virus 40 transcription in vitro by T antigen" J. VIROL. (1992), 66(7), 4591-6, XP002107330 see abstract; figure 5 ---	1-12, 15-23
Y	ZERRAHN J ET AL: "Protective immunity in BALB/c mice against the simian virus 40-induced mKSA tumor resulting from injection of recombinant large T antigen. Requirement of CD8+ T lymphocytes." JOURNAL OF IMMUNOLOGY, (1996 MAY 15) 156 (10) 3919-24. JOURNAL CODE: IFB. ISSN: 0022-1767., XP002107331 United States see figure 1 ---	13,14
Y	SUGANO S ET AL: "Use of an epitope-tagged cDNA library to isolate cDNAs encoding proteins with nuclear localization potential." GENE, (1992 OCT 21) 120 (2) 227-33. JOURNAL CODE: FOP. ISSN: 0378-1119., XP002107332 Netherlands see abstract; figure 1 ---	13,14
A	SCHIRMBECK R ET AL: "Stress protein (hsp73)-mediated, TAP-independent processing of endogenous, truncated SV40 large T antigen for Db-restricted peptide presentation." EUROPEAN JOURNAL OF IMMUNOLOGY, (1997 AUG) 27 (8) 2016-23. JOURNAL CODE: EN5. ISSN: 0014-2980., XP002107333 GERMANY: Germany, Federal Republic of cited in the application ---	
A	SCHIRMBECK R ET AL: "Peptide transporter-independent, stress protein-mediated endosomal processing of endogenous protein antigens for major histocompatibility complex class I presentation." EUROPEAN JOURNAL OF IMMUNOLOGY, (1994 JUL) 24 (7) 1478-86. JOURNAL CODE: EN5. ISSN: 0014-2980., XP002107334 GERMANY: Germany, Federal Republic of -----	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/ 06298

Box I Observations where certain claims wer found unsearchable (Continuation of item 1 of first sh et)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 26,27,36,37
are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/EP 98/06298

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9319091 A	30-09-1993	AU 3739393 A	21-10-1993
		CA 2132321 A	30-09-1993

WO

15

REC'D 04 JAN 2001
WIPO PCT

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
C 2086 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP98/06298	02/10/1998	[02/10/1998]
International Patent Classification (IPC) or national classification and IPC		
C12N15/62		
Applicant		
REIMANN, Hansjörg et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06/04/2000	28.12.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer van Heusden, M Telephone No. +49 89 2399 8145

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP98/06298

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-39 as originally filed

Claims, No.:

1-37 with telefax of 19/10/2000

Drawings, sheets:

1/7-7/7 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5, 13-14, 24, 26-27, 31-32, 34-37
	No:	Claims	6-12, 15-23, 25, 28-30, 33
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-37
Industrial applicability (IA)	Yes:	Claims	1-25, 28-35
	No:	Claims	26-27, 36-37 (?)

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Additional r marks to s ction V:

1. Citations

The documents mentioned in this IPER are numbered as in the International Search Report (ISR), i.e. D1 corresponds to the first document of the ISR etc.

2. Novelty (Article 33(2) PCT)

2.1 The present application discloses a polynucleotide encoding a fusion protein which is stable in a cell, said fusion protein comprising a first (poly)peptide which as such is unstable in a cell, and a second (poly)peptide which co-precipitates a chaperone. It further relates to a vector and a host cell comprising said polynucleotide and to a method of producing said fusion protein, the first (poly)peptide thereof, or a complex thereof. It also relates to a method for producing antibodies against said first (poly)peptide and a method of immunizing. It further relates to a kit, a diagnostic composition and a pharmaceutical composition comprising said fusion protein , the encoding polynucleotide or an antibody to the fusion protein.

2.2 The subject matter of claims 1-5 satisfies the criterion set forth in Article 33(2) PCT. Documents D2 and D3 do not relate to a polynucleotide encoding a fusion protein comprising a first polypeptide which is unstable in a cell. Both documents relate to a fusion protein of GST, which is soluble.

2.3 However, claim 6 relates to a polynucleotide encoding a fusion protein comprising any first polypeptide and a second polypeptide which is a viral T antigen carrying an internal and/or C-terminal deletion..D2 discloses a polynucleotide encoding a fusion protein of GST (first polypeptide) and viral SV40 T antigen fragment encoding amino acids 1-272 (thus deleted at the C-terminal) (p. 11, l. 17-23). Said fusion protein further comprises an IgG binding domain of protein A which is considered a tag (p. 3, l. 13-17) and optionally a protease cleavage site (p. 2, l. 1-7 and claims 8-10). D2 also discloses a polynucleotide encoding said fusion protein, in a vector comprising an expression control sequence, in a prokaryotic host cell (p. 11, l. 17 - p. 12, l. 11). The fusion protein is produced recombinantly

and separated by SDS-PAGE which inherently separates the fusion protein from the complexed chaperones. D2 further discloses thrombin cleavage of the fusion protein (p. 13, l. 28-32). D2 also discloses a kit (or diagnostic composition) comprising the fusion protein (p. 7, l. 1-5). D2 further discloses a method of contacting the fusion protein with an antibody (p. 14, l. 29 - p. 15, l. 15). A pharmaceutical composition of e.g. the fusion protein can be interpreted as the fusion protein in saline or water, which is also disclosed in D2.
Thus D2 anticipates the subject matter of claims 6-12, 15-23, 25, 28-30 and 33.

2.4 Moreover, document D3 discloses a construct similar to that disclosed in D2, namely encoding a fusion protein of GST, a tag, and the 1-272 fragment of SV40 TAg (Fig. 5A and the abstract). Said fusion protein is expressed in E. coli. Therefore also D3 anticipates the subject matter of claims 6-12, 15 and 17-23.

3. Inventive step (Article 33(3) PCT)

3.1 The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject matter of claims 1-6, 24, 26-27 and 34-37 does not involve an inventive step in view of document D7.
D7 discloses the tight binding of cT-Ag to hsp73 (in fact D6 (on p. 2018, right column, paragraph 2) discloses that cT-Ag associates with hsp73 for more than 6 hours, whereas other proteins associate with hsp73 only transiently, i.e. < 1 h). It seems that the stabilizing effect of hsp73 demonstrated in the present application is based on the strong interaction between cT-Ag and hsp73. Especially in view of the vague definition of 'co-precipitating' in the description (p. 6: 'in general, an interaction ... that leads to precipitation... upon interaction .. with a specific precipitating agent...'), it appears doubtful whether any other (poly)peptide 'co-precipitating' hsp73 will enable increased stability of a fusion protein.
Similarly, it is questionable whether binding to any chaperone, other than hsp73, will result in increased stability of a fusion protein to which it is complexed. It is even more doubtful whether any chaperone will enable a humoral immune response, antibody production or vaccination. It appears that the numerous chaperones (including the GrpE family of chaperones) have differing functions and that not necessarily any chaperone enables the presentation of peptides to CTL.
Therefore the IPEA considers that the subject matter of claims 1-6, 24, 26-27 and

34-37 does not solve the problem of the present invention over the entire breadth of the claims.

3.2 D7 discloses the binding of cT-Ag and T272 to hsp73. It further suggests that hsp73 transports cT-Ag into a subcellular compartment where this protein is degraded. Thus D7 in fact teaches away from the hypothesis that complexing with hsp73 may result in increased stability of fusion proteins. Thus an inventive step can be recognized for a polynucleotide encoding a fusion protein of a first unstable protein and cT-Ag (or T272) which binds hsp73. Thus the subject matter of claims 12 or 13, insofar as they are dependent on claim 4, could be considered inventive.

3.3 Document D7 discloses a cytoplasmic TAg variant (cT-Ag) which lacks an internal fragment comprising at least part of the NLS, more specifically residues 110-152, and which still complexes with the hsp73 chaperone (p. 1484, right column, 48-51 and Fig. 2). Thus it is obvious for the skilled person that said region can be removed without affecting the ability of the fusion protein to complex with the chaperone. Therefore the subject matter of claims 13-14 lacks an inventive step.

3.4 Claims 31-32 do not include any additional matter that could render them inventive as such. Thus they would be allowable only in combination with a novel and inventive main claim.

4. Industrial applicability (Article 33(4) PCT)

4.1 The subject matter of claims 1-25 and 28-35 is industrially applicable.

4.2 The subject matter of claims 26-27 and 36-37 includes methods of treatment of the human or animal body and is thus excluded from examination by Article 34(4)(a)(i) PCT in combination with Rule 67(iv) PCT. For the assessment of these claims on the question whether they are industrially applicable, no unified criteria exist in PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment

and the use of such a compound for the manufacture of a medicament for a new medical treatment.
The applicant is already informed that in the case of a European application, claims 26-27 and 36-37 are not allowable because 'methods of treatment of human or animal body by surgery or by therapy and diagnostic methods practised on the human or animal body shall not be regarded as inventions which are susceptible of industrial application'.

Additional remarks to section VIII:

The following objections are raised under **Article 6 PCT** concerning the clarity of the claims:

1. The subject matter of claims 1-11 and 13-6 lacks clarity in that the polynucleotide appears insufficiently characterized by technical features. According to Article 6 PCT in combination with Rule 6.3 PCT the claims shall define the matter for which protection is sought in terms of technical features. The IPEA considers that a peptide, polypeptide, protein, oligonucleotide, gene, etc..., being chemical products, must be characterized clearly and unambiguously by their amino acid and/or nucleic acid sequences, i.e. by reference to their specific SEQ ID NO. The characterization of a polypeptide only by the desired function (i.e. co-precipitating chaperones) is not clear, especially in view of the vague wording '**co-precipitating**'. It is well known in the art that precipitation depends largely on the affinity of the precipitating agent and on the precipitation conditions. Co-precipitation will depend on the affinity between the polypeptide and, in this case, the chaperone. Thus in the absence of a clear definition of the second (poly)peptide, by technical features or by unambiguous functional features, the subject matter of claims 1-16 is considered to lack clarity.

2. Claim 25 lacks clarity in that it refers to a chaperone as defined in claim 4 or 5, whereas claims 3 and 4 relate to a chaperone.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

VOSSIUS & PARTNER
Siebertstrasse 4
D-81675 Munich
ALLEMAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	28.12.2000
Applicant's or agent's file reference C 2086 PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP98/06298	02/10/1998	02/10/1998

Applicant
REIMANN, Hansjörg et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Papiol Rovira, M Tel.+49 89 2399-7199

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
C 2086 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP98/06298	02/10/1998	02/10/1998
International Patent Classification (IPC) or national classification and IPC C12N15/62		
Applicant REIMANN, Hansjörg et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06/04/2000	28.12.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer van Heusden, M Telephone No. +49 89 2399 8145

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP98/06298

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-39 as originally filed

Claims, No.:

1-37 with telefax of 19/10/2000

Drawings, sheets:

1/7-7/7 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2.and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5, 13-14, 24, 26-27, 31-32, 34-37
	No:	Claims	6-12, 15-23, 25, 28-30, 33
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-37
Industrial applicability (IA)	Yes:	Claims	1-25, 28-35
	No:	Claims	26-27, 36-37 (?)

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Additional remarks to section V:

1. Citations

The documents mentioned in this IPER are numbered as in the International Search Report (ISR), i.e. D1 corresponds to the first document of the ISR etc.

2. Novelty (Article 33(2) PCT)

2.1 The present application discloses a polynucleotide encoding a fusion protein which is stable in a cell, said fusion protein comprising a first (poly)peptide which as such is unstable in a cell, and a second (poly)peptide which co-precipitates a chaperone. It further relates to a vector and a host cell comprising said polynucleotide and to a method of producing said fusion protein, the first (poly)peptide thereof, or a complex thereof. It also relates to a method for producing antibodies against said first (poly)peptide and a method of immunizing. It further relates to a kit, a diagnostic composition and a pharmaceutical composition comprising said fusion protein , the encoding polynucleotide or an antibody to the fusion protein.

2.2 The subject matter of claims 1-5 satisfies the criterion set forth in Article 33(2) PCT. Documents D2 and D3 do not relate to a polynucleotide encoding a fusion protein comprising a first polypeptide which is unstable in a cell. Both documents relate to a fusion protein of GST, which is soluble.

2.3 However, claim 6 relates to a polynucleotide encoding a fusion protein comprising any first polypeptide and a second polypeptide which is a viral T antigen carrying an internal and/or C-terminal deletion. D2 discloses a polynucleotide encoding a fusion protein of GST (first polypeptide) and viral SV40 T antigen fragment encoding amino acids 1-272 (thus deleted at the C-terminal) (p. 11, l. 17-23). Said fusion protein further comprises an IgG binding domain of protein A which is considered a tag (p. 3, l. 13-17) and optionally a protease cleavage site (p. 2, l. 1-7 and claims 8-10). D2 also discloses a polynucleotide encoding said fusion protein, in a vector comprising an expression control sequence, in a prokaryotic host cell (p. 11, l. 17 - p. 12, l. 11). The fusion protein is produced recombinantly

and separated by SDS-PAGE which inherently separates the fusion protein from the complexed chaperones. D2 further discloses thrombin cleavage of the fusion protein (p. 13, l. 28-32). D2 also discloses a kit (or diagnostic composition) comprising the fusion protein (p. 7, l. 1-5). D2 further discloses a method of contacting the fusion protein with an antibody (p. 14, l. 29 - p. 15, l. 15). A pharmaceutical composition of e.g. the fusion protein can be interpreted as the fusion protein in saline or water, which is also disclosed in D2.
Thus D2 anticipates the subject matter of claims 6-12, 15-23, 25, 28-30 and 33.

2.4 Moreover, document D3 discloses a construct similar to that disclosed in D2, namely encoding a fusion protein of GST, a tag, and the 1-272 fragment of SV40 TAg (Fig. 5A and the abstract). Said fusion protein is expressed in E. coli.
Therefore also D3 anticipates the subject matter of claims 6-12, 15 and 17-23.

3. Inventive step (Article 33(3) PCT)

3.1 The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject matter of claims 1-6, 24, 26-27 and 34-37 does not involve an inventive step in view of document D7.
D7 discloses the tight binding of cT-Ag to hsp73 (in fact D6 (on p. 2018, right column, paragraph 2) discloses that cT-Ag associates with hsp73 for more than 6 hours, whereas other proteins associate with hsp73 only transiently, i.e. < 1 h). It seems that the stabilizing effect of hsp73 demonstrated in the present application is based on the strong interaction between cT-Ag and hsp73. Especially in view of the vague definition of 'co-precipitating' in the description (p. 6: 'in general, an interaction ... that leads to precipitation... upon interaction .. with a specific precipitating agent...'), it appears doubtful whether any other (poly)peptide 'co-precipitating' hsp73 will enable increased stability of a fusion protein.
Similarly, it is questionable whether binding to any chaperone, other than hsp73, will result in increased stability of a fusion protein to which it is complexed. It is even more doubtful whether any chaperone will enable a humoral immune response, antibody production or vaccination. It appears that the numerous chaperones (including the GrpE family of chaperones) have differing functions and that not necessarily any chaperone enables the presentation of peptides to CTL.
Therefore the IPEA considers that the subject matter of claims 1-6, 24, 26-27 and

34-37 does not solve the problem of the present invention over the entire breadth of the claims.

3.2 D7 discloses the binding of cT-Ag and T272 to hsp73. It further suggests that hsp73 transports cT-Ag into a subcellular compartment where this protein is degraded. Thus D7 in fact teaches away from the hypothesis that complexing with hsp73 may result in increased stability of fusion proteins. Thus an inventive step can be recognized for a polynucleotide encoding a fusion protein of a first unstable protein and cT-Ag (or T272) which binds hsp73. Thus the subject matter of claims 12 or 13, insofar as they are dependent on claim 4, could be considered inventive.

3.3 Document D7 discloses a cytoplasmic TAg variant (cT-Ag) which lacks an internal fragment comprising at least part of the NLS, more specifically residues 110-152, and which still complexes with the hsp73 chaperone (p. 1484, right column, 48-51 and Fig. 2). Thus it is obvious for the skilled person that said region can be removed without affecting the ability of the fusion protein to complex with the chaperone. Therefore the subject matter of claims 13-14 lacks an inventive step.

3.4 Claims 31-32 do not include any additional matter that could render them inventive as such. Thus they would be allowable only in combination with a novel and inventive main claim.

4. Industrial applicability (Article 33(4) PCT)

4.1 The subject matter of claims 1-25 and 28-35 is industrially applicable.

4.2 The subject matter of claims 26-27 and 36-37 includes methods of treatment of the human or animal body and is thus excluded from examination by Article 34(4)(a)(i) PCT in combination with Rule 67(iv) PCT. For the assessment of these claims on the question whether they are industrially applicable, no unified criteria exist in PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment

and the use of such a compound for the manufacture of a medicament for a new medical treatment.
The applicant is already informed that in the case of a European application, claims 26-27 and 36-37 are not allowable because 'methods of treatment of human or animal body by surgery or by therapy and diagnostic methods practised on the human or animal body shall not be regarded as inventions which are susceptible of industrial application'.

Additional remarks to section VIII:

The following objections are raised under **Article 6 PCT** concerning the clarity of the claims:

1. The subject matter of claims 1-11 and 13-6 lacks clarity in that the polynucleotide appears insufficiently characterized by technical features. According to Article 6 PCT in combination with Rule 6.3 PCT the claims shall define the matter for which protection is sought in terms of technical features. The IPEA considers that a peptide, polypeptide, protein, oligonucleotide, gene, etc..., being chemical products, must be characterized clearly and unambiguously by their amino acid and/or nucleic acid sequences, i.e. by reference to their specific SEQ ID NO. The characterization of a polypeptide only by the desired function (i.e. co-precipitating chaperones) is not clear, especially in view of the vague wording '**co-precipitating**'. It is well known in the art that precipitation depends largely on the affinity of the precipitating agent and on the precipitation conditions. Co-precipitation will depend on the affinity between the polypeptide and, in this case, the chaperone. Thus in the absence of a clear definition of the second (poly)peptide, by technical features or by unambiguous functional features, the subject matter of claims 1-16 is considered to lack clarity.

2. Claim 25 lacks clarity in that it refers to a chaperone as defined in claim 4 or 5, whereas claims 3 and 4 relate to a chaperone.

PCT/EP98/06298
REIMANN, Hansjörg et al.
Our Ref.: C 2086 PCT

Claims

1. A polynucleotide encoding a fusion protein which is stable in a cell, said fusion protein comprising:
   (a) a first (poly)peptide which as such is unstable in a cell; and
   (b) a second (poly)peptide which co-precipitates a chaperone.

2. The polynucleotide of claim 1, wherein said first (poly)peptide is or comprises an epitope and/or a functional and/or structural domain of a protein, and/or a mutated or truncated variant of a protein.

3. The polynucleotide of claims 1 or 2, wherein said chaperone belongs to the family of heat shock protein (hsp)70 chaperones.

4. The polynucleotide of claim 3, wherein said chaperone is hsp73.

5. The polynucleotide of any one of claims 1 to 4, wherein said second (poly)peptide is a viral T antigen carrying an internal and/or C-terminal deletion.

6. A polynucleotide encoding a fusion protein which is stable in a cell, said fusion protein comprising a first (poly)peptide and a second (poly)peptide which is a viral T antigen carrying an internal and/or C-terminal deletion.

7. The polynucleotide of claim 5 or 6, wherein the function and/or structure of the N-terminal J domain of said viral T antigen is maintained.

8. The polynucleotide of any one of claims 5 to 7, wherein said viral T antigen is a viral large T antigen.

9. The polynucleotide of any one of claims 5 to 7, wherein said viral T antigen is SV40 T antigen.

10. The polynucleotide of claim 8, wherein said viral large T antigen is SV40 large T antigen.

11. The polynucleotide of claim 10, wherein the about 300 C-terminal amino acids of said SV40 large T antigen are deleted.

12. The polynucleotide of claim 10 or 11, wherein said SV40 large T antigen contains amino acids 1 to 272.

13. The polynucleotide of any one of claims 10 to 12, wherein the internal deletion comprises at least part of the nuclear localisation signal.

14. The polynucleotide of claim 13, wherein amino acids 110 to 152 are deleted.

15. The polynucleotide of any one of claims 1 to 14 further encoding a tag.

16. The polynucleotide of any one of claims 1 to 15, wherein said first and second (poly)peptide are linked via a protease cleavage site.

17. A vector comprising the polynucleotide of any one of claims 1 to 16.

18. The vector of claim 17, wherein said polynucleotide is operatively linked to an expression control sequence.

19. A host cell comprising the polynucleotide of any one of claims 1 to 16, or the vector of claim 17 or 18.

20. The host cell of claim 19 which is a eukaryotic or prokaryotic cell.

21. A method for the production of the fusion protein as defined in any one of claims 1 to 16, said method comprising:
    (a) culturing the host cell of claim 19 or 20 under conditions that allow the synthesis of said fusion protein; and

(b) recovering said fusion protein from the culture.

22. The method of claim 21 further comprising the step of separating said fusion protein from complexed chaperones.

23. A fusion protein encoded by the polynucleotide of any one of claims 1 to 16, or the vector of claim 17 or 18, or obtainable or obtained by the method of claim 21 or 22.

24. A method for the production of a first (poly)peptide as defined in claim 1 or 2, said method comprising:
(a) culturing the host cell of claim 19 or 20 under conditions that allow the synthesis of a fusion protein as defined in claim 16;
(b) recovering said fusion protein from the culture; and
(c) separating said second (poly)peptide from said fusion protein by proteolytic cleavage.

25. A method for the production of a complex comprising the fusion protein of claim 23 and a chaperone as defined in claim 4 or 5, said method comprising:
(a) culturing the host cell of claim 19 or 20 under conditions that allow complex formation of said fusion protein with said chaperone; and
(b) recovering said complex from the culture.

26. A method for the production of an antibody directed against a first (poly)peptide as defined in claim 1 or 2, said method comprising administering in an amount sufficient to induce a humoral immune response the polynucleotide of any one of claims 1 to 16, the vector of claim 17 or 18, the fusion protein of claim 23, the first (poly)peptide obtainable or obtained by the method of claim 24, and/or the complex obtainable or obtained by the method of claim 25 to a subject.

27. A method of immunizing a subject, said method comprising administering in an amount sufficient to induce a humoral and/or cellular immune response the polynucleotide of any one of claims 1 to 16, the vector of claim 17 or 18, the fusion protein of claim 23, the first (poly)peptide obtainable or obtained by the

method of claim 24, and/or the complex obtainable or obtained by the method of claim 25 to said subject.

28. A kit comprising:
    (a) the polynucleotide of any one of claims 1 to 16;
    (b) the vector of claim 17 or 18;
    (c) the host cell of claim 19 or 20;
    (d) the fusion protein of claim 23;
    (e) the first (poly)peptide obtainable or obtained by the method of claim 24;
    (f) the complex obtainable or obtained by the method of claim 25; and/or
    (g) the antibody obtainable or obtained by the method of claim 26.

29. A diagnostic composition comprising the polynucleotide of any one of claims 1 to 16, the vector of claim 17 or 18, the fusion protein of claim 23, the first (poly)peptide obtainable or obtained by the method of claim 24, the complex obtainable or obtained by the method of claim 25, and/or the antibody obtainable or obtained by the method of claim 26.

30. A method for the detection of the presence of an epitope comprised in a (poly)peptide as defined in claim 1 or 2, said method comprising:
    (a) contacting the fusion protein of claim 23 or the first (poly)peptide obtainable or obtained by the method of claim 24 with an antibody or a cytotoxic T-lymphocyte (CTL) under conditions that allow binding of said antibody or CTL to said epitope; and
    (b) detecting whether the antibody or CTL has bound to said epitope.

31. The method of claim 30, wherein said antibody or CTL is derived from an individual infected with a pathogen.

32. The method of claim 30 or 31, wherein the first (poly)peptide of said fusion protein or said first (poly)peptide obtainable or obtained by the method of claim 24 is derived from a pathogen.

33. A pharmaceutical composition comprising the polynucleotide of any one of claims 1 to 16, the vector of claim 17 or 18, the fusion protein of claim 23, the first (poly)peptide obtainable or obtained by the method of claim 24, the complex obtainable or obtained by the method of claim 25, and/or the antibody obtainable or obtained by the method of claim 26, and, optionally, a pharmaceutically acceptable carrier and/or diluent.

34. The pharmaceutical composition of claim 33 which is a vaccine.

35. The pharmaceutical composition of claim 34, wherein said vaccine induces a humoral and/or cellular immune response.

36. Use of the polynucleotide of any one of claims 1 to 16 or the vector of claim 17 or 18 for the production of an antibody directed against a first (poly)peptide as defined in claim 1 or 2.

37. Use of a (poly)peptide comprising an epitope detected by the method of any one of claims 30 to 32 or a complex produced by the method of claim 25 for the production of an antibody.

PATENT COOPERATION TREAT

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
VOSSIUS & PARTNER
Postfach 86 07 67
D-81634 München
GERMANY

EINGEGANGEN
Vossius & Partner
19. Juli 1999
Frist
Dearb..

Applicant's or agent's file reference C 2086 PCT	Date of mailing *(day/month/year)* 12/07/1999 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/EP 98/06298	International filing date *(day/month/year)* 02/10/1998
Applicant REIMANN, Hansjörg et al.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Sandra De Jong-van Dam

Form PCT/ISA/220 (July 1998)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
C 2086 PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 98/ 06298	02/10/1998	
Applicant		
REIMANN, Hansjörg et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[X] furnished subsequently to this Authority in written form.

[X] furnished subsequently to this Authority in computer readble form.

[X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

METHOD FOR THE PRODUCTION OF (POLY)PEPTIDES BY USING TRUNCATED VARIANTS OF THE SV40 LARGE T ANTIGEN WITH AN INTACT N TERMINUS

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/06298

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 26,27,36,37 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
T/EP 98/06298

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/62 C07K14/025 C07K16/08 C07K16/18 G01N33/50
C12Q1/68 A61K39/295

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K G01N C12Q A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	SCHIRMBECK R. ET AL: "Truncated or chimeric endogenous protein antigens gain immunogenicity for B cells by stress protein-facilitated expression." EUROPEAN JOURNAL OF IMMUNOLOGY, (MAY 1999) 29/5 (1740-1749)., XP002107329 see the whole document	1-25,27, 30
X	WO 93 19091 A (AMRAD CORP LTD) 30 September 1993 see page 4, last paragraph - page 5, paragraph 1 see page 11 see page 14-17	1-12, 15-25,30
Y	see page 19; claims 8-10	13,14
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 June 1999	12/07/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Espen, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	COULOMBE, JOSEE ET AL: "Activation of simian virus 40 transcription in vitro by T antigen" J. VIROL. (1992), 66(7), 4591-6, XP002107330 see abstract; figure 5 ---	1-12, 15-23
Y	ZERRAHN J ET AL: "Protective immunity in BALB/c mice against the simian virus 40-induced mKSA tumor resulting from injection of recombinant large T antigen. Requirement of CD8+ T lymphocytes." JOURNAL OF IMMUNOLOGY, (1996 MAY 15) 156 (10) 3919-24. JOURNAL CODE: IFB. ISSN: 0022-1767., XP002107331 United States see figure 1 ---	13,14
Y	SUGANO S ET AL: "Use of an epitope-tagged cDNA library to isolate cDNAs encoding proteins with nuclear localization potential." GENE, (1992 OCT 21) 120 (2) 227-33. JOURNAL CODE: FOP. ISSN: 0378-1119., XP002107332 Netherlands see abstract; figure 1 ---	13,14
A	SCHIRMBECK R ET AL: "Stress protein (hsp73)-mediated, TAP-independent processing of endogenous, truncated SV40 large T antigen for Db-restricted peptide presentation." EUROPEAN JOURNAL OF IMMUNOLOGY, (1997 AUG) 27 (8) 2016-23. JOURNAL CODE: EN5. ISSN: 0014-2980., XP002107333 GERMANY: Germany, Federal Republic of cited in the application ---	
A	SCHIRMBECK R ET AL: "Peptide transporter-independent, stress protein-mediated endosomal processing of endogenous protein antigens for major histocompatibility complex class I presentation." EUROPEAN JOURNAL OF IMMUNOLOGY, (1994 JUL) 24 (7) 1478-86. JOURNAL CODE: EN5. ISSN: 0014-2980., XP002107334 GERMANY: Germany, Federal Republic of -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 98/06298

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9319091 A	30-09-1993	AU 3739393 A	21-10-1993
		CA 2132321 A	30-09-1993